dedication to the public of the subject matter of the claims as previously presented. Moreover, an issue of new matter is not raised by these amendments and entry thereof is respectfully requested.

In view of the preceding amendments and remarks, Applicants respectfully request reconsideration and withdrawal of the outstanding rejections.

Election/Restriction

Restriction to one of the allegedly independent and distinct inventions is required under 35 U.S.C. § 121:

Group I: Claims 1, 4, 5, and 7, drawn to nucleic acids from influenza virus and DNA sequences complementary to these nucleic acids;

Group II: Claims 8, 22, 25 and 26, drawn to nucleic acids and polynucleotides of influenza virus, specifically M, PB1, PA, PB2, HA and NA, sequences;

Group III: Claims 12, 23, and 27, drawn to a vaccine comprising a reassortant influenza virus, cold-adapted wild type NA and HA proteins; and

Group IV: Claims 19 and 20, drawn to methods for the prevention and treatment of influenza virus infection.

The Office alleged that the inventions were distinct, each from the other, for the following reasons. The inventions of Groups I and II are allegedly unrelated because it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions or they have different effects. The inventions of Groups I and II are drawn to different nucleic acid sequences derived from influenza strains, in particular, both inventions include variant sequences of the PB2 gene.

The Office also alleged that the inventions of Groups III and IV are related as product and process of use. However, the inventions can be shown to be distinct if either or the both can be shown: (1) the process for using the product as claimed can be practiced with another materially different product; or (2) the product as claimed can be used in a materially different process of

using that product. In the instant case, it is alleged that the invention of Group III is drawn to a vaccine for influenza A virus and the invention of Group IV is drawn to a method of the treatment of influenza A virus infection. It was further alleged that treatment and prevention of an influenza A infection need not be performed with the product of invention III and prevention of said infection is alleged to be possible with a multiple of unique vaccines such as subunit vaccines or inactivated vaccines.

The Office alleged that because the inventions are distinct for the reasons provided above and have acquired a separate status in the art, restriction for examination was required.

During a February 7, 1997 telephone conference with the undersigned attorney, a provisional election was made with traverse, to prosecute the invention of Group III, claims 12, 23, and 27. Applicants' undersigned attorney confirms the election, with traverse, to prosecute the invention of Group III, claims 12, 23 and 27. However, withdrawal of the requirement for restriction is respectfully requested, between the inventions of Groups II and III, claims 8, 12, 22, 23, and 25-27 for the following reasons.

Under MPEP §808, the Examiner must examine the subject application on the merits even though it includes claims to distinct inventions, if the search and examination of the application can be made without serious burden. There are two criteria for a proper requirement for restriction, namely, 1) the inventions must be independent or distinct, and 2) there must be a serious burden on the Examiner if restriction is not required.

Applicants maintain that it would not be a serious burden on the Examiner to search and examine the inventions of Groups II and III. The invention of Group II is drawn to nucleic acid and polynucleotides of influenza virus and the invention of Group III is directed to vaccines comprising the polynucleotides that are the subject of the invention of Group II. Therefore, a search of the art for the polynucleotides of Group II would necessarily reveal the invention of Group III, i.e., vaccines comprising these polynucleotides. Therefore, the search and examination of the invention of Group II with Group III would not be a serious burden on the Examiner.

In addition, pursuant to MPEP §802.01, "'independent' (i.e., not dependent) means that there is no disclosed relationship between the two or more subjects disclosed, that is, they are unconnected in design, operation or effect...." Clearly, there is a disclosed relationship between the polynucleotides of Group II and the vaccines comprising these polynucleotides, i.e., the invention of Group III.

Accordingly, in view of the preceding discussion, Applicants respectfully assert that two or more independent and distinct inventions have not been claimed in the subject application because Groups II and III are not independent under MPEP §802.01. Therefore, restriction is not proper under 35 U.S.C. §121.

Furthermore, assuming that the Examiner is correct in requiring restriction for dependent but distinct inventions, Applicants maintain that the inventions are not distinct. Under MPEP §802.01, distinct inventions are related, "but are capable of separate manufacture, use or sale as claimed...." The inventions of Groups II and III are not capable of separate manufacture in that each requires some of the same polynucleotides.

In view of the preceding remarks, Applicants maintain that the allegedly distinct inventions are not distinct. Therefore, under MPEP §803, a restriction requirement is not proper between the inventions of Groups II and III.

35 U.S.C. § 112, Second Paragraph

Claim 27 was rejected under 35 U.S.C. § 112, second paragraph on the ground that there is insufficient basis for the phrase "comprising the nucleic acid sequence of claim 25" in claim 27. The claim also was rejected on the ground that the actual reassortant virus should be stated and that reassortant is misspelled. In view of the amendment of claim 27 as noted above, reconsideration and withdrawal of the rejection is respectfully requested.

Claim 12 was rejected under this statutory provision on the ground that the term "the polynucleotides being operatively linked" does not clearly define what linkage is required. The

Office alleged that the sequences could be physically ligated in order to function as polycistronic units or alternatively be so assembled in proximity to one another as found in the viral nucleocapsid structure. In view of the amendments to claim 12, above, reconsideration and withdrawal of the rejection of claim 12 is respectfully requested.

35 U.S.C. § 112, First Paragraph

The specification stands objected to for allegedly failing to enable claim 12 and 27. Although the Office Action fails to state which claims the specification is alleged to enable, it appears from the remarks that the Office intended to reject claims 12 and 27 drawn to vaccines.

The Office stated that the specification fails to enable one of skill in the art to assemble the relevant components, i.e., the polynucleotides of the claimed invention in order to produce a viable virus. Applicants respectfully traverse.

The subject specification set forth the complete nucleotide sequences for the claimed polynucleotide components. Page 4, lines 18-21 teaches that to produce the vaccines of the present invention, a cold-adapted reassortant vaccine strain is passed once to prepare a virus seed lot which is used to produce vaccine pools. Page 27 through page 38 set forth specific examples to prepare vaccine pools. This information, in combination with the knowledge available to the skilled artisan, enables the claimed invention. It is a well-settled tenet of patent law that an application need not teach, and preferably omits what is known in the art. See, *e.g., Hybritech v. Monoclonal Antibodies,* 231 USPQ 81 (Fed. Cir. 1986), *cert. denied,* 480 U.S. 947 (1987). The Office has provided an issued United States patent that was filed and issued prior to the effective filing date of the subject invention as evidence of the state of the art of influenza viral engineering techniques. Because this technology is described in the subject application and details regarding influenza engineering were in the art at the time the parent application was

filed, Applicants have enabled the claimed invention. For this reason, the objection to the specification and the rejection of the claims are improper and should therefore be withdrawn.

35 U.S.C. § 102

Claims 12 and 27 stand rejected under 35 U.S.C. § 102, for allegedly being anticipated by Cox et al. The Cox et al. reference is cited for teaching the identification of sequence changes in the cold-adapted (ca), live attenuated vaccine, A/Ann Arbor/6/60 (H2N2) and a mutated version. The Office alleged that the polynucleotide represented in sequence ID number 15, the PB2 encoding sequence, is presented in Figure 6, page 563 of this reference. Applicants respectfully traverse.

The amended claims under consideration all require the presence of mutated PB2 of the progenitor virus, the sequence of which is provided in Seq. ID No. 15. Mutated PB2 has critical differences at nucleotide positions 141, 821 and 1933 as compared to prior art sequences. In comparison to Cox et al, the base at position 1933 is thymidine while Applicants claim cytosine at position 1933 of the PB2 polynucleotide. Accordingly, Cox et al. does not anticipate the claimed invention. Applicants respectfully request reconsideration and withdrawal of the rejection of the claims under 35 U.S.C. § 102.

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Claims 12, 23, and 27 stand rejected under 35 U.S.C. § 103, as allegedly unpatentable over the disclosures of Cox et al. and Maassab et al. (1982). The Office alleged that Cox et al. teaches an approach for producing live attenuated influenza vaccines using a cold-adapted mutant donor strain. The reference is alleged to teach sequence information for six genes of both

the wt and ca mutant in Figures 5 and 6 as well as that five or six internal genes are derived from the ca A/Ann Arbor/6/60 parental virus strain.

Maassab et al. is cited for teaching that in experiments with recombinant virus derived from the cold-adapted A/Ann Arbor/6/60 (H2N2) in ferrets were attenuated and genetically stable. The cold-adapted strain was seen to be unable to replicate in the test animal lungs and grew to lower titers in the nasal turbinates in contrast to the wild-type virus.

It was alleged that it would have been obvious to one of ordinary skill in the art at the time the invention was made to produce a live influenza A vaccine using a cold-adapted "master" strain or parental strain and to incorporate its ca qualities into a clinically relevant strain by mating and reassortant methodology. The initial master strain was alleged to have been created by the incorporation/rescue of these sequences into a helper virus with selection to create the cold-adapted master strain. Applicants respectfully traverse.

Neither Cox et al. nor Maassab et al. teaches or suggests the sequence of the PB2 gene manufactured and successfully sequenced by Applicants. This sequence is provided in SEQ ID NO 15. No wild-type human viruses or reported sequences have cytosine at position 1933, which the Applicants note, is believed to be critical to the cold-adapted phenotype (see page 10, lines 1 to 10, of the specification.)

MPEP § 2142 sets for the criteria for a *prima facie* case of obviousness under 35 U.S.C. § 103. This section recites in part:

> "To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed invention and the reasonable expectation of success must be found in the prior art, and not based on applicant's disclosure."

MPEP § 2142, bridging paragraph of pages 108-109 (Rev. 2, July 1996).

Applicants submit that the Office has failed to establish a *prima facie* case of obviousness under 35 U.S.C. § 103. The Office has not acknowledged the difference in the sequence of the PB2 polynucleotide, as compared to prior published sequences. Accordingly, the Office also has failed to establish the motivation to modify the teachings of the prior art references which is required to arrive at Applicants' claimed invention. Specifically, the Office has failed to establish where in the references the suggestion lies to modify PB2 to arrive at a sequence identified by Applicants as SEQ. ID NO. 15 (PB2). None of the prior art references, alone or in combination with each other, teaches or suggests that this single nucleotide change would produce a temperature-sensitive and cold-adapted phenotype useful for the production of a vaccine. None of the prior art provides the motivation to mutate position 1933 to further attenuate the virus for the production of a vaccine. Without the teaching of the specific mutations that provide the attenuated virus for a vaccine (and as claimed by Applicants) or even that further mutations may be desired or required, the teachings fail to render obvious the claimed invention. Applicants therefore respectfully request reconsideration and withdrawal of the rejection of the claims under 35 U.S.C. § 103.

III. CONCLUSION

If a telephone interview would be of assistance in advancing prosecution of this invention, the Examiner is invited to telephone the undersigned attorney at the number provided below. In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this

document to **Deposit Account No. 03-1952**. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: May 14, 1997

Respectfully submitted,

By: _____

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dedication to the public of the subject matter of the claims as previously presented. Moreover, an issue of new matter is not raised by these amendments and entry thereof is respectfully requested.

In view of the preceding amendments and remarks, Applicants respectfully request reconsideration and withdrawal of the outstanding rejections.

Election/Restriction

Restriction to one of the allegedly independent and distinct inventions is required under 35 U.S.C. § 121:

Group I: Claims 1, 4, 5, and 7, drawn to nucleic acids from influenza virus and DNA sequences complementary to these nucleic acids;

Group II: Claims 8, 22, 25 and 26, drawn to nucleic acids and polynucleotides of influenza virus, specifically M, PB1, PA, PB2, HA and NA, sequences;

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The Office alleged that the inventions were distinct, each from the other, for the following reasons. The inventions of Groups I and II are allegedly unrelated because it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions or they have different effects. The inventions of Groups I and II are drawn to different nucleic acid sequences derived from influenza strains, in particular, both inventions include variant sequences of the PB2 gene.

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III. CONCLUSION

If a telephone interview would be of assistance in advancing prosecution of this invention, the Examiner is invited to telephone the undersigned attorney at the number provided below. In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this

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Dated: May 14, 1997

Respectfully submitted,

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